

CASE REPORT

DRESS syndrome: A case of cross-reactivity with lacosamide?

*Man Kei Fong, and *Bun Sheng

Epilepsia Open, 2(2):273–275, 2017
doi: 10.1002/epi4.12053



Dr. Man Kei Fong is a neurologist working in the Princess Margaret Hospital in Hong Kong.

SUMMARY

A 42-year-old patient with epilepsy was admitted to the hospital for fever and generalized skin rash. He has known allergy to phenytoin. Valproate was started in 2012, but failed to control his seizure despite gradual increase in dosage. Phenobarbitone was added 16 days before admission and was stopped on admission. He was treated with beta-lactam antibiotics. The rash subsided gradually after the cessation of phenobarbitone. Lacosamide was subsequently added for seizure control. Unfortunately, he developed drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome soon after introduction of lacosamide that required the use of systemic steroid for acute hepatitis. A cross-reactivity with lacosamide was suspected in view of the rapid onset of DRESS syndrome after the initial rash resolution and soon after the introduction of lacosamide. We postulated that the rapid onset of DRESS syndrome may be related to the aromatic ring that is in common among phenytoin, phenobarbitone, and lacosamide.

KEY WORDS: Lacosamide, DRESS syndrome, Cross reactivity.

CASE REPORT

A 42-year-old Chinese man (with unknown HLA-B1502 status) was admitted to Princess Margaret Hospital on April 23, 2016, for skin rash. He first presented with recurrent focal seizures (facial paresthesia and aphasia) in 2012. Computed tomography (CT) of the brain showed 7 × 5 cm left frontoparietal astrocytoma. It was partially excised in 2012. Subsequent brain imaging showed static residual tumor size. Regarding his seizure control, he was put on phenytoin in 2012, but developed skin rash. He was then put

on valproate. However, he experienced frequent seizures despite high valproate dose. There was not much improvement after the addition of levetiracetam. Phenobarbitone was added to replace levetiracetam. He developed low-grade fever and generalized maculopapular skin rash 16 days after starting phenobarbitone. Initial blood tests, including white cell count, renal and liver function tests, were normal. Empirical amoxicillin/clavulanate were given. Phenobarbitone was stopped in view of suspected drug rash. Septic workups, including blood, urine, and sputum cultures, were negative. Procalcitonin level was not high. He had focal seizures during hospitalization while on valproate monotherapy. Lumbar puncture showed normal cerebrospinal fluid parameters. HIV serology was negative. Phenobarbitone allergy was suspected in view of the temporal relationship, the negative septic workup, and the history of phenytoin allergy. His fever and rash gradually subsided over a few days (Fig. 1).

Because he had frequent seizure attacks during admission, lacosamide was added by an on-call doctor. Unfortunately, he developed generalized maculopapular rash (Fig. 2) and fever again 1 day later (8 days after admission). Repeated blood tests showed raised aminotransferase (ALT 105 U/L), normal bilirubin and alkaline

Accepted February 27, 2017.

*Department of Medicine and Geriatrics, Princess Margaret Hospital, Kowloon, Hong Kong

Address correspondence to Fong Man Kei, Department of Medicine and Geriatrics, Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Lai Chi Kok, Kowloon, Hong Kong. E-mail: keison722@hotmail.com

Practical Implication: In patients with known hypersensitivity to anti-convulsants bearing an aromatic ring, the use of lacosamide may require extra caution.

© 2017 The Authors. *Epilepsia Open* published by Wiley Periodicals Inc. on behalf of International League Against Epilepsy.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEY POINTS

- Early recognition and management of DRESS syndrome is important
- The use of lacosamide in a patient with allergy to aromatic anticonvulsants may need extra caution

phosphatase (ALP), normal renal function, and normal white cell count. Lacosamide was stopped immediately. Nevertheless, his skin rash progressed in the next few days. Serial blood tests showed evidence of acute liver injury (peak ALT 1,481 U/L, ALP 305 U/L, bilirubin 20 μ mol/L, international normalized ratio [INR] 1.4, NH₃ 107 μ mol/L), leukocytosis (peak total white cell count 31.9×10^9 /L), neutrophilia (peak 13.4×10^9 /L), monocytosis (peak 4.4×10^9 /L), lymphocytosis with atypical lymphocyte (peak 12.6×10^9 /L), and eosinophilia (1.9×10^9 /L). The overall picture was compatible with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Valproate was stopped owing to acute liver failure. Gabapentin was given for seizure control. Oral prednisolone 30 mg bd was added 13 days after admission (5 days after recurrence of skin rash) owing to significant clinical deterioration despite the cessation of lacosamide. His condition gradually improved afterward. Fever/skin rash subsided. Liver function and white cell counts gradually normalized. Oral prednisolone was tapered off over 4 weeks. His seizures were well controlled with gabapentin monotherapy upon his last visit with us 4 weeks after discharge. He was taken care of by our neurosurgeons thereafter.

DISCUSSION

DRESS syndrome is a rare yet severe idiosyncratic drug reaction characterized by fever, rash, and abnormal white cell count together with internal organs involvement. It

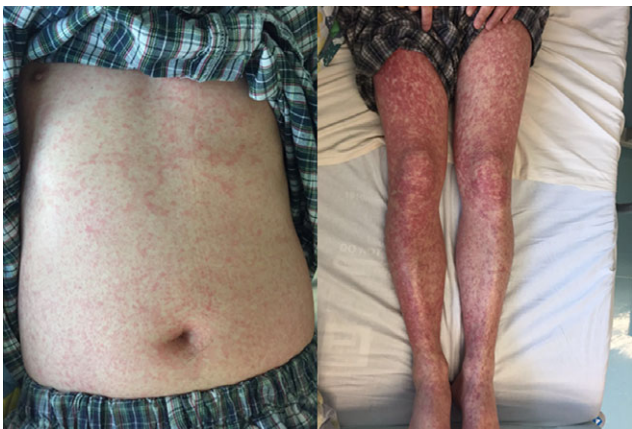


Figure 2.
The skin rash developed after lacosamide.
Epilepsia Open © ILAE

typically occurs 2–8 weeks after starting the causative drug. Anticonvulsants, especially aromatic anticonvulsants like phenytoin, are one of the common causes. Treatment is largely supportive, with immediate cessation of the causative drug. Steroids were commonly used for severe cases, but their role is still controversial.¹

The development of DRESS syndrome soon after the resolution of initial fever and rash led to a careful review of the potential culprit. The patient was given beta-lactum antibiotics during admission, yet the resolution of DRESS syndrome despite ongoing antibiotic treatment made them much less likely to be the culprit. There are a few case reports on valproate-induced DRESS syndrome, but overall it is still very rare. Moreover, the long history of valproate exposure (since 2012), the initial resolution of skin rash despite taking valproate, and the rapid development of DRESS syndrome soon after the administration of lacosamide probably favored a cross-reactivity to lacosamide. We postulated that the cross-reactivity could be related to the aromatic ring on lacosamide, which is a common structure found in phenytoin and phenobarbitone as well. The

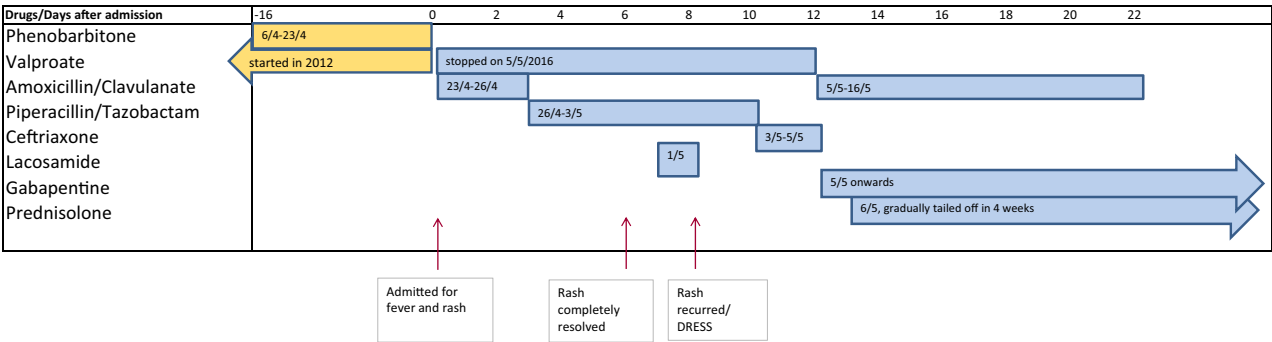


Figure 1.
Temporal relationship between the used drugs and the skin rash/DRESS.
Epilepsia Open © ILAE

introduction of lacosamide challenged the initially resolved allergic response, leading to a more fulminant presentation of drug allergy.

The choice of anticonvulsant depends on a variety of factors, including the type of seizure, drug response, side effects, and patient comorbidities. This patient was a good example to demonstrate the rational selection of anticonvulsant. Patient had a history of phenytoin allergy in 2012 and was admitted for suspected phenobarbitone allergy in April 2016. It is well known that aromatic anticonvulsants (e.g., phenytoin, carbamazepine, phenobarbitone) could have high chance of cross-reactivity.² The development of DRESS syndrome soon after lacosamide in this patient was highly suggestive of cross-reactivity, although it was rarely reported.³ We did not rechallenge the patient with lacosamide to confirm the hypersensitivity because of the potential devastating consequence. Skin-prick test for lacosamide is also not available clinically.

In summary, DRESS syndrome is a rare but severe reaction that requires immediate attention. The use of lacosamide in a patient with previous allergy to aromatic anticonvulsants may require extra caution.

DISCLOSURE

We have nothing to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Choudhary S, McLeod M, Torchia D, et al. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. *J Clin Aesthet Dermatol* 2013;6:31–37.
2. Wang XQ, Lang SY, Shi XB, et al. Cross-reactivity of skin rashes with current antiepileptic drugs in Chinese population. *Seizure* 2010;19:562–566.
3. Koubeissi MZ, Vismer M, Ehrlich A. Lacosamide-induced rash. *Epileptic Disord* 2014;16:380–383.